

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 May 2003 (15.05.2003)

PCT

(10) International Publication Number
WO 03/039609 A1

(51) International Patent Classification⁷: A61L 27/32,
27/42, C25D 13/02, 13/20, A61F 2/30

(21) International Application Number: PCT/GB02/04889

(22) International Filing Date: 28 October 2002 (28.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0126467.0 3 November 2001 (03.11.2001) GB

(71) Applicant (for all designated States except US): ACCENTUS PLC [GB/GB]; 329 Harwell, Didcot, Oxfordshire OX11 0QJ (GB).

(72) Inventors; and

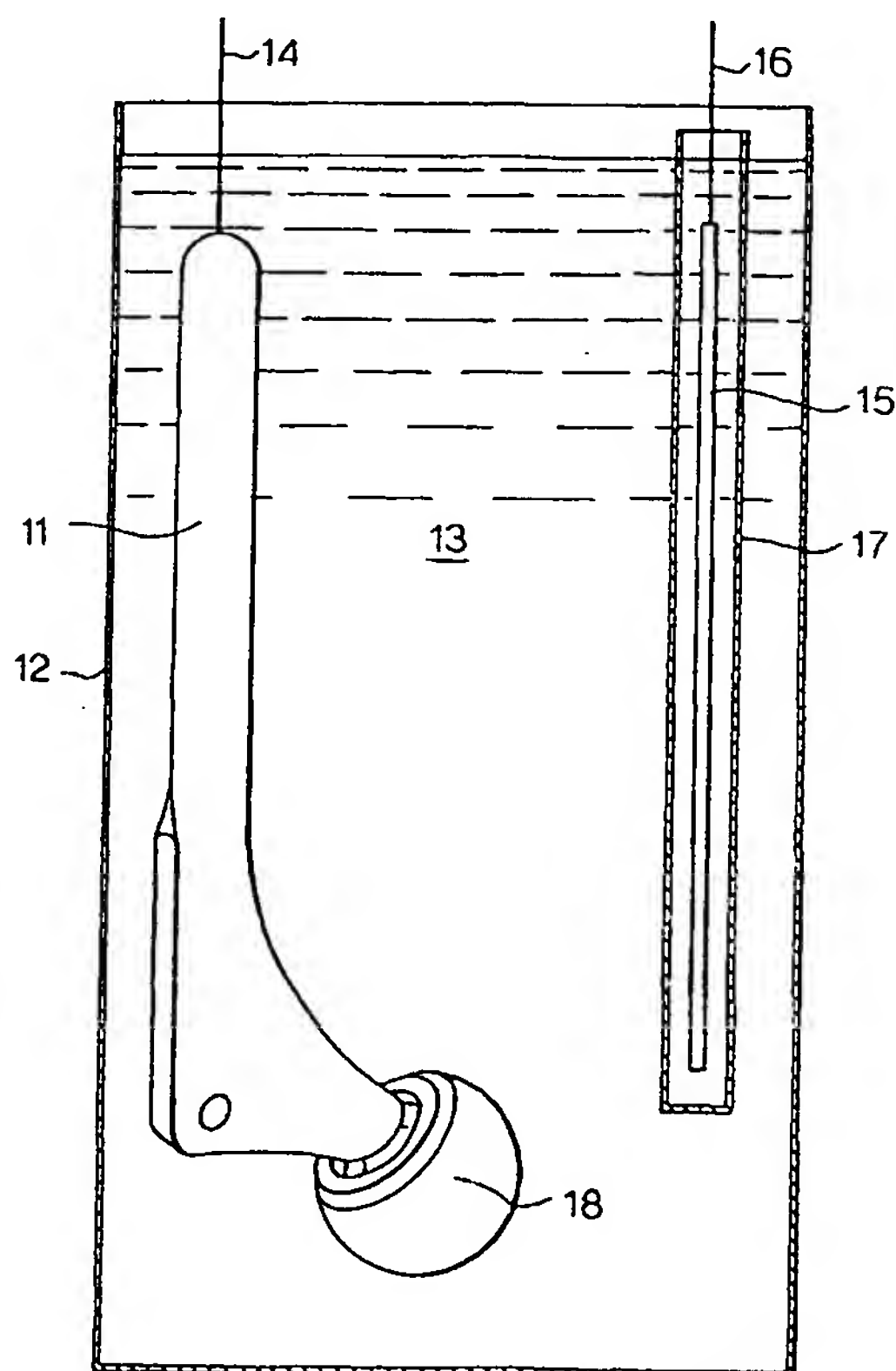
(75) Inventors/Applicants (for US only): PICKFORD, Martin, Edward, Lee [GB/GB]; 37 Downland Close, Locks Heath, Southampton, Hampshire SO31 6WB (GB). SEGAL, David, Leslie [GB/GB]; 43 Foxborough Road, Radley, Abingdon, Oxfordshire OX14 3AB (GB). TURNER, Andrew, Derek [GB/GB]; 17 Loyd Close, Abingdon, Oxfordshire OX14 3TE (GB).

(74) Agents: TALBOT-PONSONBY, Clare, Josephine et al.; Accentus plc, Patent Dept., 329 Harwell, Didcot, Oxfordshire OX11 0QJ (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,

[Continued on next page]

(54) Title: DEPOSITION OF COATINGS ON SUBSTRATES



(57) Abstract: A two (or more) stage process is described for electrochemically coating a material comprising calcium phosphate onto an electrically conducting substrate, in particular the electrophoretic deposition of a coating of calcium phosphate, such as hydroxyapatite, on an electrically conducting substrate (such as a bone replacement prosthesis). Surface preparation, precoating and protection precautions are provided to achieve acceptable bond strength for the coating.

WO 03/039609 A1



SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD,

SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— of inventorship (Rule 4.17(iv)) for US only

Published:

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

- 1 -

Deposition of coatings on substrates

The invention relates to the deposition of calcium phosphate onto a bone replacement prosthesis and more particularly the deposition of calcium phosphate coated vesicles, or droplets having a hydrophobic core coated with calcium phosphate, onto electrically conducting substrates and in particular metallic bone replacement prostheses or parts thereof.

10

Patent specification W0 00/00177 describes a vesicle comprising an inner layer which comprises a phospholipid and an outer layer which comprises calcium phosphate. The vesicles may contain pharmaceutically active compounds including compounds which assist the binding of the coating to existing bone (bone growth factors), treat a specific bone disease or any diseased region adjacent to bone, or relieve pain. There is also described a droplet comprising a hydrophobic core, an inner layer which comprises a surfactant, and an outer layer which comprises calcium phosphate. W0 00/00177 also describes a method for producing such vesicles or hydrophobic droplets and a method for depositing such vesicles or droplets on an electrically conducting substrate. The method is referred to as electrolytic deposition but is perhaps more accurately described as electrophoretic deposition.

While this deposition method can be carried out at low enough temperatures to avoid degrading the contents of the vesicles or droplets, a problem is achieving satisfactory adhesion of the deposited material to the substrate.

It is an object of the present invention to overcome or ameliorate this problem. It is a further object of

- 2 -

this invention to provide more generally a method of preparing an electrically conducting substrate and depositing a coating thereon so as to achieve good distribution and adhesion of the coating on the
5 substrate.

The invention provides in one of its aspects a method for producing an adherent coating of a coating material comprising calcium phosphate on an electrically
10 conducting substrate, which method comprises first exposing the substrate to an electrochemical surface pre-treatment using a solution comprising water for removing contaminants and/or effecting a surface conversion and/or applying a primary coating to form a surface layer or
15 surface compound layer adapted to bond to a subsequently deposited coating, and depositing upon the pre-treated surface the coating material by an electrochemical deposition process from a solution comprising calcium and phosphate ions or a suspension of calcium phosphate
20 particles in liquid.

In a preferred embodiment, the electrochemical surface pre-treatment is a treatment for removing contaminants and/or effecting a surface conversion.
25 Preferably the pre-treatment comprises effecting a surface conversion.

The electrically conducting substrate may be any substrate which conducts electricity or which has a
30 conducting surface. The substrate is preferably metal, more preferably titanium, a titanium alloy or a cobalt/chromium alloy, most preferably a titanium alloy.

The electrochemical surface pre-treatment may
35 comprise electrochemical etching to dissolve a thin surface layer of the substrate surface. Preferably,

- 3 -

where the method is applied to a metal substrate, the electrolyte composition and impressed electrical current are selected so as to reveal the micro-structure of the metal by dissolving the grain boundaries at a faster rate and thereby roughen the surface. Mineral acid electrolyte will normally be suitable, with a complexant, such as fluoride, where the substrate metal is titanium. Application of ultrasound and/or current reversal is effective for creating a suitably rough surface.

10

The electrochemical surface pre-treatment takes place using a solution comprising water as a solvent. The solution may comprise a mixture of solvents including water. Preferably the solution comprises at least 20% water, more preferably 50% water, more preferably 70% and most preferably 90% or more of water. In a particularly preferred embodiment, an aqueous solution is used and water is the only solvent. In a preferred embodiment the solution is an aqueous phosphate electrolyte.

20

During the surface conversion, the surface of the electrically conducting substrate may be converted, for example, into an oxide, a metal salt or a mixed oxide and metal salt to form a layer that is integral with the surface of the substrate. The oxide is typically a hydrous oxide. Where the surface conversion layer is a mixture of oxide and metal salts, both the oxide and the metal salt are derived from the metal of the substrate. The metal salt is typically insoluble in water.

30

Where the electrically conducting substrate is titanium or a titanium alloy then the surface conversion may convert the surface of the metal to form an oxide film on which calcium phosphate is deposited in the electrochemical deposition step of the process. The surface conversion layer may also be a mixed oxide and

35

- 4 -

titanium salt layer where the titanium salt is one that is insoluble in water. For example, a mixed oxide and phosphate layer can be formed when phosphoric acid is used in the surface conversion process.

5

Where the electrically conducting substrate is a cobalt/chromium alloy, the surface conversion may be achieved by dissolving the surface of the substrate in a phosphate medium in order to form metal phosphate salts on the surface of the substrate.

The electrochemical deposition process may comprise electrophoretic deposition of particulate material from a suspension thereof in liquid, or electrocoagulation, or electroprecipitation from a solution of a desired coating material or precursor therefor, or electrolytic deposition from a solution of a desired coating material or precursor therefor.

More than one electrochemical deposition process may be used to build a series of coating layers chosen, for example, to optimise binding efficiency of one layer upon the immediately preceding layer.

A pre-treatment surface coating, or the deposited coating, or one or more of the deposited coating layers may be subjected to a plasma fusing action. This is conveniently achieved by allowing the applied voltage to rise as the surface coating or coating layer deposits on the substrate and raises the electrical resistance across the substrate surface, such that plasma forms in pores of the deposited coating and thereby generates heat sufficient to melt and fuse the coating. In this way increased coating density(if wanted) and adhesion to the substrate can be achieved.

- 5 -

The method according to the invention has particular application to the coating onto a substrate electrically conducting surface of vesicles comprising an inner phospholipid coated with an outer layer of calcium phosphate or of droplets comprising an inner hydrophobic core coated with an outer layer of calcium phosphate.

In one embodiment, prior to the electrophoretic deposition of the calcium phosphate or the said vesicles or droplets, one or more interlayers is provided on the cleaned and roughened metal surface. The first interlayer is the surface conversion layer. For certain metals, such as titanium, the surface conversion coating layer can conveniently be in the form of an adherent oxide film produced by anodic polarisation. Periodic polarity reversal may be applied to increase the thickness of the oxide film layer formed. As an alternative, a phosphate conversion layer can be formed in phosphoric acid.

20

For certain metals, such as a cobalt/chromium alloy, it is important to avoid corrosion of the metal surface as this not only will undercut subsequent coatings, but also introduce corrosion products into the coating. The presence of such corrosion products may be undesirable for a bone replacement prosthesis where the corrosion products may subsequently leach into body fluids or tissue. A suitable protective interlayer on cobalt/chromium alloy can be provided by surface dissolution into a neutral/alkaline phosphate solution which creates an adherent insoluble phosphate layer which forms the surface conversion layer. It is typically advantageous to use polarity reversal when forming a surface conversion layer on a cobalt/chromium alloy.

35

A graduation of coating properties through the

- 6 -

thickness of the coating may be engineered by appropriate control of coating conditions such as particle size, zeta potential, applied electrical potential, pH, temperature. This may conveniently be achieved by using multiple
5 immersion tanks. For example, a hydroxyapatite coating may be laid down on a surface conversion coating, and on this an outer layer of hydroxyapatite vesicles. The inner layer of hydroxyapatite may be subjected to a plasma treatment as described above to increase its density and
10 adhesion to the substrate. Such an inner layer provides a strongly adherent key onto which hydroxyapatite vesicles (which need to be deposited without significant heating as explained in WO 00/00177) can then be deposited by electrophoresis. This process may also be performed for
15 other forms of calcium phosphate or using other forms of calcium phosphate as the coating layer.

Insoluble Hydroxyapatite is the form of calcium phosphate required when resorption into body fluids is to
20 be avoided. In certain circumstances, it is specifically desired to provide a coating, or part of a coating, which is resorbable into body fluids. In that case conditions of deposition are chosen which deposit calcium phosphate in a different, soluble, form.

25

Coating layers grown so as to have columnar pores, with control of the pore diameter and length, may be used to provide a reservoir within the pores for pharmaceutically active compounds, such as antibiotics,
30 pain relief agents, etc.

Control of the fluid viscosity, surface charge and water solubility can provide for progressive release of an active agent diffusing out of the coating.

35

The passage of the electrophoretic deposition

- 7 -

current can sometimes result in the production of gas bubbles at a substrate metal surface, particularly in aqueous media. This is undesirable as bubble growth can disrupt the coating and/or the presence of the bubbles adversely affects the adhesion of the coating. To avoid this, there is preferably included in the deposition suspension a sacrificial component, that is a component which is easily reduced at a cathode or oxidised at an anode (whichever is required) to create a water soluble rather than a gaseous product. An alternative approach is to use liquids which comprise organic solvents, for example alcohols, glycols or ketones.

Calcium phosphate is soluble in acidic media. As described in WO 00/00177 calcium phosphate in solution is caused to crystallise around a vesicle or droplet using ultrasonics to disperse a water immiscible solvent phase containing the dissolved pharmaceutically active agent to create dispersed droplets around which the calcium phosphate forms a coating. We have found that calcium phosphate crystal formation is improved in this process by progressively reducing the solution acidity. This action to raise the pH of the solution may be achieved by chemical reaction such as introduction at a controlled rate of formaldehyde into nitric acid, or by electrodialytic action in which anions are replaced with hydroxyls, or by electrolytic action such as nitrate reduction at a cathode. These processes for changing the pH can also aid the deposition of calcium phosphate particles from a suspension.

Normally, the perturbation of pH at the depositing surface encourages the suspended fine particles to coagulate onto the roughened substrate metal surface, thus creating an adherent layer. For this, it is important to optimise the conditions of the ions of

- 8 -

calcium, phosphate, complexant and the pH of the solution. Further improvement of the bond strength between the deposited particles may be achieved by incorporating soluble resins (polycarboxylic acids) in the solution. These may either dry out to create an increased bond strength, or be cross-linked in-situ through reactions occurring at the substrate surface. The polymeric materials used would need to be biocompatible for implant applications. Organically modified ceramics may also be included as part of the suspension to provide a key onto which the polymer could bind, as well as creating an environment encouraging the formation of a stable structure around the vesicles or droplets.

15

In a further embodiment, the present invention provides a method for producing an adherent coating of a coating material comprising vesicles on an electrically conducting substrate, which method comprises first exposing the substrate to an electrochemical surface pre-treatment for removing contaminants and/or effecting a surface conversion and/or applying a primary coating to form a surface layer or surface compound layer adapted to bond to a subsequently deposited coating, and depositing upon the pre-treated surface by an electrochemical deposition process a coating material comprising vesicles comprising an inner phospholipid coated with an outer layer of calcium phosphate. Preferably the electrochemical surface pre-treatment is a treatment for removing contaminants and/or effecting a surface conversion layer or the pre-treatment comprises effecting a surface conversion layer. Preferably the electrochemical deposition process is electrophoretic deposition. The electrochemical pre-treatment may take place in any solvent or solvent mixture, such as an organic solvent including one or more of an alcohol,

30
35

- 9 -

glycol or ketone, or water or a mixture thereof.

The invention includes a substrate when provided with a surface coating by a method as aforesaid.

5

A specific example of a method embodying the invention will now be described with reference to the drawing filed herewith, which is a diagrammatic representation of a hip implant prosthesis undergoing
10 treatment in an electrochemical treatment bath.

In this example, hip prosthesis 11 is made of titanium and is shown in an electrochemical bath 12 filled with appropriate treatment solution or electrolyte
15 13. The prosthesis 11 is connected via lead 14 to an appropriate source of electrical potential. Electrode 15 is connected via lead 16 to the source of electrical potential. There is also provided a membrane 17 encompassing the electrode 15 for use when the electrode
20 15 is connected to a positive potential and it is required to protect the prosthesis 11 from any ions dissolved into the electrolyte 13 from the electrode 15. The membrane 17 may have to be removed when a negative potential is applied to electrode 15.

25

Parts of the prosthesis 11, primarily the ball joint 18, which are not to be coated are provided with a protective insulating layer, for example of tape. For the first operation to remove contaminants from the metal
30 surface of the titanium prosthesis 11, a surface layer of the metal is electrolytically removed using an acid bath containing fluoride with the prosthesis 11 connected to a positive electrical potential supply and the electrode 15 connected to the negative supply. Application of
35 ultrasound to the bath and/or periodic current reversal helps to introduce surface roughness during this process.

- 10 -

With a suitable change in bath conditions and polarity, the second stage creation of an adherent oxide film on the titanium prosthesis 11 takes place. This is
5 the surface conversion coating. If phosphoric acid is present in the bath then a mixed phosphate and oxide surface conversion coating is formed.

The prosthesis 11 is then moved to another bath, or
10 the bath 12 is washed out and its contents replaced, to provide a solution containing calcium and phosphate ions, and a potential applied to deposit a layer of hydroxyapatite on to the clean titanium surface. At this stage nitrate may be included in the solution as a
15 sacrificial component to prevent the release of gas bubbles from the titanium surface.

To densify this layer of hydroxyapatite and improve its adhesion to the substrate prosthesis 11, the applied
20 deposition voltage is allowed to rise as the layer thickness increases (and the surface electrical resistance increases correspondingly), such that plasma forms in the pores of deposited hydroxyapatite and generates sufficient heat to cause melt fusing onto the
25 substrate.

In the final step, a treatment suspension 13 is provided which contains vesicles, each of which comprises an inner layer which comprises a phospholipid and an
30 outer layer which comprises calcium phosphate. The vesicles may contain pharmaceutically active compounds including compounds which assist the binding of the coating to existing bone (bone growth factors), treat a specific bone disease or any diseased region adjacent to
35 bone, or relieve pain. A potential is applied to deposit a coating layer of hydroxyapatite vesicles which bond to

- 11 -

the interlayer of hydroxyapatite applied in the previous stage. During this deposition temperature rise is controlled, ideally to maintain temperature close to ambient so as not to damage constituents of the vesicles.

5

In this way adhesion of the coatings with a static shear strength of at least 15 Mpa can be achieved.

The invention is not restricted to the details of the foregoing example. For instance the method may be applied to other metal prostheses made, for example of an alloy of cobalt and chromium. The prosthesis provided with a simple layer of strongly adherent hydroxyapatite (ie without vesicles) has usefulness in its own right, although the strong bonding at low temperature of hydroxyapatite vesicles is a key characteristic of the product of the example. The latter can be deposited directly onto the first conversion layer (titanium oxide) of the prosthesis, if desired.

20

The final stage deposition need not necessarily be of vesicles as described, but may be of droplets having any hydrophobic core encased in calcium phosphate.

Incorporation of other elements by substitution in the calcium phosphate may be desirable. The other elements are preferably alkaline earth metals, more preferably magnesium, strontium or barium or a mixture thereof. For example, substituted magnesium can act to promote bone growth, or substituted strontium can affect adhesion, or the retention or release of a drug contained in the vesicles.

The method has application for other electrically conducting substrates and other coating materials. A particular advantage of electrophoretic deposition and

35

- 12 -

other electrochemical deposition processes, used for depositing electrically insulating coatings, is that the deposited layer is self levelling. This is because the resistance of thick regions reduces current flow in those regions and thus encourages greater deposition in regions where the coating is thinner.

Thus, for example, the method has particular value for providing a uniform thickness coating on a corrugated, or similar uneven surface, such as a catalyst coating on a corrugated metal (eg FECRALLOY steel) substrate.

- 13 -

Claims

1. A method for producing an adherent coating of a coating material comprising calcium phosphate on an electrically conducting substrate, which method comprises first exposing the substrate to an electrochemical surface pre-treatment using a solution comprising water for removing contaminants and/or effecting a surface conversion and/or applying a primary coating to form a surface layer or surface compound layer adapted to bond to a subsequently deposited coating, and depositing upon the pre-treated surface the coating material by an electrochemical deposition process from a solution comprising calcium and phosphate ions or a suspension of calcium phosphate particles in liquid.
2. A method as claimed in claim 1, wherein the electrochemical surface pre-treatment comprises electrochemical etching to dissolve a thin surface layer of the substrate surface.
3. A method as claimed in claim 2, applied to a metal substrate, wherein, the electrolyte composition and impressed electrical current are selected so as to reveal the micro-structure of the metal by dissolving the grain boundaries at a faster rate and thereby roughen the surface.
4. A method as claimed in claim 2 or claim 3, wherein ultrasound and/or current reversal is applied to assist the creation of a rough surface on the etched substrate metal surface.
5. A method as claimed in any of the preceding claims, wherein the electrochemical deposition process comprises electrophoretic deposition of particulate material from a

- 14 -

suspension thereof in liquid.

6. A method as claimed in any of claims 1 to 4, wherein the electrochemical deposition process comprises
5 electrocoagulation.

7. A method as claimed in any of claims 1 to 4, wherein the electrochemical deposition process comprises electroprecipitation from a solution of a desired coating
10 material or precursor therefor.

8. A method as claimed in any of claims 1 to 4, wherein the electrochemical deposition process comprises electrolytic deposition from a solution of a desired
15 coating material or precursor therefor.

9. A method as claimed in any of the preceding claims, wherein more than one electrochemical deposition process is used to build a series of coating layers.
20

10. A method as claimed in any of the preceding claims, wherein a pre-treatment surface coating, or the deposited coating, or one or more of the deposited coating layers is subjected to a plasma fusing action.
25

11. A method as claimed in in any of claims 1 to 10, wherein the pre-treatment comprises treating the substrate to remove surface contaminants and the coating comprises an inner phospholipid coated with an outer
30 layer of calcium phosphate or of droplets comprising an inner hydrophobic core coated with an outer layer of calcium phosphate.

12. A method as claimed in any of the preceding claims,
35 wherein, prior to the electrophoretic deposition of the coating, one or more interlayers is provided on the

- 15 -

cleaned and roughened metal surface.

13. A method as claimed in claim 12, wherein the
substrate metal comprises titanium and the first
5 interlayer is a conversion coating layer in the form of
an adherent oxide film produced by anodic polarisation.

14. A method as claimed in claim 12, wherein the
substrate metal comprises titanium and the first
10 interlayer is a phosphate conversion layer formed in
phosphoric acid.

15. A method as claimed in claim 12, wherein the
substrate metal comprises a cobalt/chromium alloy and the
15 first interlayer comprises an adherent insoluble
phosphate layer provided by surface dissolution into a
neutral/alkaline phosphate solution.

16. A method as claimed in any of the preceding claims,
20 wherein a hydroxyapatite coating is laid down on the
surface conversion coating, and on the hydroxyapatite
layer an outer layer of hydroxyapatite vesicles is
applied.

25 17. A method as claimed in any of the preceding claims,
wherein coating layers are grown so as to have columnar
pores to provide a reservoir within the pores for
pharmaceutically active compounds.

30 18. A method as claimed in any of the preceding claims,
wherein there is included in the deposition suspension a
sacrificial component to create a water soluble rather
than a gaseous product as a result of any electrolytic
action at the surface of the substrate metal.

35

19. A method as claimed in any of the preceding claims,

- 16 -

wherein the solution or liquid comprises one or more alcohols, glycols or ketones.

20. A method as claimed in any of the preceding claims,
5 wherein soluble polycarboxylic acid is incorporated in the solution or liquid.

21. A method as claimed in claim 20, wherein organically
10 modified ceramics are included as part of the suspension to provide a key onto which the polycarboxylic acid binds.

22. A method as claimed in any of the preceding claims
15 wherein the pH of the solution and/or suspension is progressively raised by chemical reaction involving introduction at a controlled rate of an appropriate chemical reagent.

23. A method as claimed in any of the preceding claims
20 wherein the pH of the solution and/or suspension is progressively raised by electrodialytic action in which anions are replaced with hydroxyls.

24. A method as claimed in any of the preceding claims
25 wherein the pH of the solution and/or suspension is progressively raised by electrolytic action.

25. A method as claimed in any of the preceding claims
30 wherein other elements are incorporated in the calcium phosphate coating by substitution.

26. A method as claimed in claim 25 wherein the other
elements are magnesium, strontium or barium or a mixture thereof.

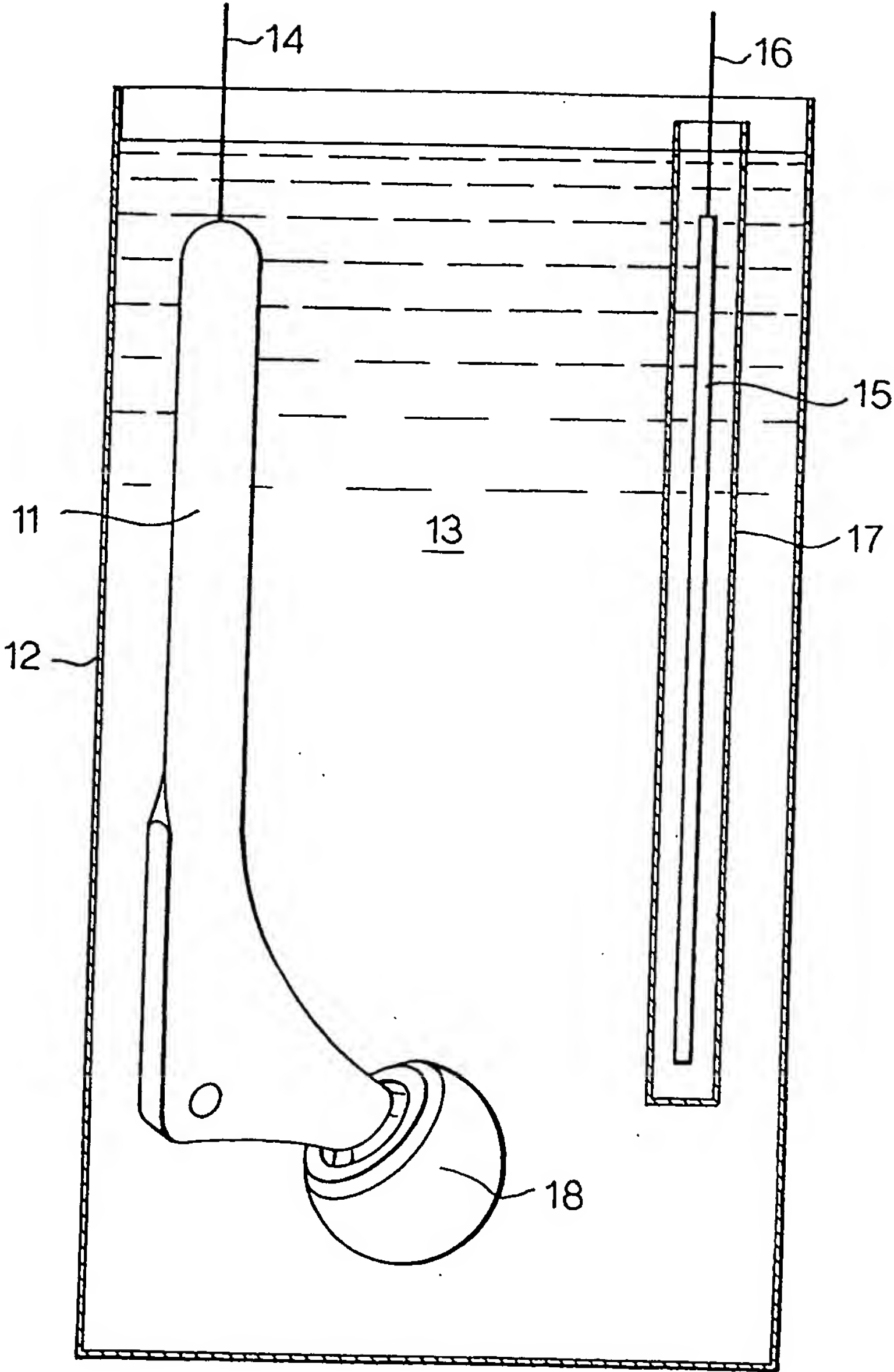
35

27. A method for producing an adherent coating of a

- 17 -

coating material comprising vesicles on an electrically
conducting substrate, which method comprises first
exposing the substrate to an electrochemical surface pre-
treatment for removing contaminants and/or effecting a
5 surface conversion and/or applying a primary coating to
form a surface layer or surface compound layer adapted to
bond to a subsequently deposited coating, and depositing
upon the pre-treated surface by an electrochemical
deposition process a coating material comprising vesicles
10 comprising an inner phospholipid coated with an outer
layer of calcium phosphate.

28. An electrically conducting substrate when provided
with a coating by a method as claimed in any of the
15 preceding claims.



INTERNATIONAL SEARCH REPORT

PCT/GB 02/04889

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61L27/32 A61L27/42 C25D13/02 C25D13/20 A61F2/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L C25D A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 00177 A (ISIS INNOVATION ; CZERNUSZKA JAN TADEUSZ (GB); HADDOW DAVID BRYAN () 6 January 2000 (2000-01-06) cited in the application examples figures claims	1-28
A	US 5 258 044 A (LEE DOSUK D) 2 November 1993 (1993-11-02) claims	1-28
A	US 5 171 326 A (DUCHEYNE PAUL ET AL) 15 December 1992 (1992-12-15) claims -/-	1-28

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

11 March 2003

Date of mailing of the international search report

19/03/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Thornton, S

INTERNATIONAL SEARCH REPORT

PCT/GB 02/04889

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MESSERSMITH ET AL: "Preparation of Calcium - Loaded Liposomes and Their Use in Calcium Phosphate Formation"</p> <p>CHEMISTRY OF MATERIALS, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US,</p> <p>vol. 10, no. 128, 1998, pages 109-116,</p> <p>XP002117645</p> <p>ISSN: 0897-4756</p> <p>the whole document</p> <p>-----</p>	1-28

INTERNATIONAL SEARCH REPORT

PCT/GB 02/04889

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0000177	A	06-01-2000	EP 1089711 A1 WO 0000177 A1 JP 2002519316 T	11-04-2001 06-01-2000 02-07-2002
US 5258044	A	02-11-1993	WO 9314718 A1	05-08-1993
US 5171326	A	15-12-1992	US 4990163 A WO 9008520 A1	05-02-1991 09-08-1990